Intraosseous versus intravenous administration of adrenaline in patients with out-of-hospital cardiac arrest: a secondary analysis of the PARAMEDIC2 placebo-controlled trial

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Abstract

Purpose: To compare the effectiveness of the intravenous (IV) and intraosseous (IO) routes for drug administration in adults with a cardiac arrest enrolled in the Pre-Hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC2) randomised, controlled trial.

Methods: Patients were recruited from five National Health Service Ambulance Services in England and Wales from December 2014 through October 2017. Patients with an out of hospital cardiac arrest who were unresponsive to initial resuscitation attempts were randomly assigned to 1 mg adrenaline or matching placebo. Intravascular access was established as soon as possible, and IO access was considered if IV access was not possible after two attempts.

Results: Among patients with out of hospital cardiac arrest, 3631 received adrenaline and 3686 received placebo. Amongst these, 1,116 (30.1%) and 1,121 (30.4%) received the study drug via the IO route. The odds ratios were similar in the IV and IO groups for return of spontaneous circulation (ROSC) at hospital handover (adjusted odds ratio (aOR) 4.07 (95% CI 3.42-4.85) and (aOR 3.98 (95% CI 2.86-5.53), p value for interaction 0.90); survival to 30 days (aOR 1.67 (1.18-2.35) versus 0.9 (0.4-2.05), P=0.18); and favourable neurological outcome (aOR 1.39 (0.93-2.06) versus 0.62 (0.23-1.67), P=0.14).

Conclusion: There was no significant difference in treatment effect (adrenaline versus placebo) on ROSC at hospital handover between drugs administered by the intraosseous route or by the intravenous route. We could not detect any difference in the treatment effect between the IV and IO routes on the longer-term outcomes of 30-day survival or favourable neurological outcome at discharge. (ISRCTN73485024)

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Key words

Cardiac arrest, cardiopulmonary resuscitation, adrenaline, intravenous, intraosseous.

Introduction

Current resuscitation guidelines recommend the delivery of drugs via the intraosseous (IO) route only if intravenous (IV) access is difficult or impossible [1]. A variety of drugs and fluids can be delivered via the IO route. Animal studies provide proof of concept that common cardiac arrest drugs such as adrenaline [2][3] and amiodarone [4], administered via the IO route reach the systemic circulation during cardiac arrest. Pharmacokinetic studies show similar peak drug concentrations (Cmax) and time to peak drug concentrations (Tmax) between drugs administered via a central vein and sternal IO [5]. Compared with peripheral IV administration, sternal and humeral IO administration resulted in similar Cmax and Tmax values [6, 7], whilst tibial IO administration appeared less effective in some [6, 8] but not all studies [4, 9]. By contrast, the effect of IO drugs on return of spontaneous circulation (ROSC) appears similar to the IV route in both hypovolaemic [3, 9] and ventricular fibrillation cardiac arrest models [8, 10, 11]. Although resuscitation guidelines favour IV rather than IO access, IO may enable more rapid delivery of resuscitation drugs: in a randomised clinical trial, the first attempt success rate was higher with the tibial IO route than with peripheral IV (or humeral IO) route [12].

Several clinical observational studies have documented an association between use of the IO route and a lower likelihood of return of spontaneous circulation (ROSC) [13-15], survival to hospital admission [13], survival to hospital discharge [14], and favourable neurological outcome [14]. In contrast, one observational study showed that rates of ROSC at the time of emergency department arrival among out-of-hospital cardiac arrest patients in whom IO access was attempted first were non-inferior to those in whom IV access was attempted first [16].

In a multicentre double-blinded controlled trial of adrenaline versus placebo in out-of-hospital cardiac arrest (PARAMEDIC-2) [17], emergency medical services (EMS) personnel delivered the study drug according to ambulance clinical practice guidelines which state that IV access should be established as soon as possible and IO should be considered if IV access is not possible after two attempts [18]. The trial, which includes patients receiving adrenaline or placebo, provides the opportunity for unique insights into the effectiveness or

otherwise of the IO route. The objective of this paper was to explore the effect of IV and IO routes for drug delivery on the primary (survival at 30 days) and secondary outcomes (ROSC at handover to hospital, survival at hospital discharge and favourable neurological outcome at hospital discharge).

Methods

Trial design and participants

PARAMEDIC2 was a multicentre double-blinded placebo-controlled trial conducted by five National Health Service (NHS) ambulance services in the United Kingdom (UK) from December 2014 to October 2017 inclusive [17]. Participants treated for out of hospital cardiac arrest who were not successfully resuscitated by means of defibrillation and/or CPR, and who met predetermined eligibility criteria were randomly allocated to either adrenaline or saline placebo. Randomisation occurred when trial paramedics opened packs containing prefilled syringes loaded with either ten 1 mg doses of adrenaline or ten doses of 0.9% saline. Trial packs and their contents were identical in appearance and carried a unique identification number. In all other respects identical paramedic resuscitation protocols were followed. Randomisation of drug packs to ambulance services was achieved using the minimisation method with an allocation ratio of 1:1. Participants, paramedics and trial staff were blinded to treatment allocation. A full description of trial methods has been previously published [19]. When IO access was attempted, no specific site was recommended by UK paramedic practice guidelines. Most UK ambulance services train their paramedics in proximal tibial, or proximal humerus IO access.

Data

The primary aim of this study was to assess the baseline characteristics and outcome measures for participants who had received two drug administration modes: IV and IO, in the PARAMEDIC2 study. The European Resuscitation Council (ERC) resuscitation guidelines and UK paramedic practice guidelines recommend the use of IO only if IV is difficult or impossible to establish [1, 18]. Data collected prior to and at the scene of the cardiac arrest include: age, gender, initial rhythm, aetiology, witnessed, bystander CPR, time from

emergency call to trial drug administration, time from emergency call to emergency medical services (EMS) personnel arrival, time from EMS personnel arrival to trial drug administration, time on scene, time transported to hospital, survival at scene, ROSC at any time and ROSC at the point of hospital handover. Analyses assessed the primary outcome: survival at 30 days, and secondary outcomes: ROSC at handover to hospital, survival at hospital discharge and favourable neurological outcome at hospital discharge. The neurological outcome was measured using a modified Rankin scale assessment (ranging from 0 [no symptoms] to 6 [death]) where a score of 0-3 inclusive was considered favourable [20].

Statistical analysis

This study was pre-specified prior to the final data lock but not defined in the statistical analysis plan. The outcomes were analysed using the modified intention-to-treat population, which excluded those with missing outcome or unspecified drug administration route data, i.e. administration by both or unspecified routes. Patients with missing covariate data were also excluded from the adjusted analysis. Baseline characteristics were summarised using mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Baseline difference was reported with 95% confidence interval (CI) and tested using t test. For categorical variables, the number and percentage of participants were detailed, and baseline difference was assessed using Chi-squared test. Fisher's exact test was not used due to a long calculation time.

Treatment effect by the routes was assessed in each of the pre-specified outcomes using unadjusted and adjusted logistic regression models. Adjustment was made for categorical variables including gender, whether a bystander commenced CPR, witness to the arrest, aetiology, initial rhythm and continuous variables including age, interval between emergency call and ambulance arrival at scene, and interval between ambulance arrival and drug administration. The interaction between two categorical variables, treatment and administration route, was tested in all models. Unadjusted and adjusted odds ratios (uOR and aOR, respectively) were reported with 95% CI, as well as p-values for the interactions.

The primary outcome was also assessed by stratification of treatment and trial drug delivery route using Kaplan-Meier plot and Cox regression. The route and treatment interaction was

assessed and the adjusted hazard ratio (aHR) with 95% CI and p-value for interaction were reported. As the proportional hazards assumption was not met, we reported the adjusted results by survival within one day and over one day. All statistical analyses were undertaken using SAS version 9.4 (SAS Institute, Cary NC).

The trial was funded by the Heath Technology Assessment Programme of the National Institute for Health Research (NIHR). The funders had no role in the trial design, data collection or analysis, or in the writing of this report. The Warwick Clinical Trials Unit undertook data management activities. The trial statisticians assume responsibility for the integrity of the data and its analysis. The NIHR Current Controlled Trials number is ISRCTN73485024.

Results

Of 8,014 participants enrolled in the study, 697 (8.7%) had missing or unclear route of drug administration data, leaving 3,631 (90.4% of those randomised to adrenaline) and 3,686 (92.2% of those randomised to placebo) on each arm. Of these, 1,116 (30.7%) and 1,121 (30.4%) in the adrenaline and placebo arms respectively received the study drug via the IO route. The rest were given the drug via the IV route. The primary outcome data were recorded for 3,629 participants (99.9%) in the adrenaline arm and 3,682 (99.9%) in the placebo arm. A CONSORT diagram illustrates the number of participants lost to follow-up for each of the four outcomes (Figure 1).

Table 1 shows the baseline characteristics of participants by IV and IO route. Trial drug was administered via IO to more young, female and unwitnessed participants with a non-shockable rhythm and a longer time to treatment. The electronic supplementary material (Table e1) reports the unadjusted outcomes according to route of administration.

Results of adjusted analyses for the trial outcomes are presented in Figure 2. The odds ratios (adrenaline versus placebo) for ROSC at hospital handover were similar in the IV (aOR 4.07 (95% CI 3.42-4.85) and IO groups (aOR 3.98 (95% CI 2.86-5.53)), p value for interaction 0.90. The confidence intervals for survival (discharge and 30 days) and favourable neurological

outcomes for IV and IO also overlapped, with no statistical evidence of an interaction. The unadjusted results are shown in the Appendix Figure 1. By removing time from ambulance arrival to drug administration from the adjusted analysis (Appendix Figure 2), the odds ratios of treatment increased in the IV route and decreased in the IO route suggesting some of the differences in the outcomes have been explained by the time interval between ambulance arrival and drug administration.

Figure 3 presents the cumulative survival to 30-days for the IV and IO routes for both adrenaline and placebo. The survival curves are higher for the IV route than for the IO route in both the adrenaline and placebo arms, but the confidence intervals overlap and there was no statistical evidence of an interaction in both periods (within and over one day survival) (adjusted Cox regression model p=0.70 and 0.50, respectively). The aHR of IV versus IO within one day survival was 1.02 (95% CI: 0.94, 1.10) in adrenaline and 1.00 (0.93, 1.08) in placebo and the aHR over one day survival was 1.30 (95% CI: 0.98, 1.72) in adrenaline and 1.08 (0.68, 1.71) in placebo.

Discussion

In this secondary analysis of the PARAMEDIC-2 trial we have shown that the treatment effect of adrenaline (versus placebo) on ROSC at hospital admission was the same when given by the IV and IO routes. We could not detect any difference in the treatment effect between the IV and IO routes on the longer-term outcomes of 30-day survival or favourable neurological outcome at discharge.

The strength of this study is that the substantial treatment effect of adrenaline on ROSC and the inclusion of a placebo arm in the PARAMEDIC-2 trial enables a robust statistical approach that adjusts reliably for the large differences in time to drug delivery between the IV and IO routes. The large treatment effect of adrenaline on ROSC will have enabled us to detect relatively small differences in the efficacy of adrenaline between the IV and IO routes of administration. Our approach of assessing for heterogeneity of treatment effects with a statistical test for interaction, rather than undertaking separate tests of treatment effect in

each sub-group follows best practice guidelines and reduces the risk of mistakenly claiming a difference where it may not exist [21].

During prehospital resuscitation, in many settings the IO route is generally attempted only after attempts at IV access have failed or if IV access is likely to be very difficult or impossible. Thus, in comparison with the IV route, the time to drug delivery with the IO route is inevitably much longer (Table 1) and, as a result of resuscitation time bias [22], the IO route appears to be associated with worse outcomes even in the placebo group. Regardless of the route of delivery, small volumes of saline (placebo) will have no effect on ROSC, and the placebo arm of the PARAMEDIC-2 trial enabled the best possible adjustment for confounding by resuscitation time bias. The gold standard for eliminating resuscitation time bias would be a randomised clinical trial (RCT) comparing the IV versus IO drug route, although such a trial would not allow the treatment arm to be blinded.

Several other observational studies have reported outcomes following IO versus IV drug delivery and except for one [16] these all report an association between IO access and decreased rate of ROSC [13-15]. In a retrospective cohort study, the clinical outcomes of 1800 OHCA patients treated by the EMS in Seattle were analysed according to the route of delivery of the first EMS drug administered (IV or IO) [13]. In multivariable adjusted analyses, compared with the IV-treated patients, the 275 IO-treated patients (15.3%), had a lower likelihood of ROSC (OR 0.67, 95% CI 0.50 to 0.88) but IO treatment was not associated with survival to discharge (OR 0.81, 95% CI 0.55 to 1.21, p=0.31) The call to vascular access interval was available for about two-thirds of the full cohort and a sensitivity analysis confined to these patients produced results that were similar to the overall cohort.

Like our study, two of the previous studies are secondary analyses of RCTs. In a secondary analysis of the Resuscitation Outcomes Consortium Prehospital Resuscitation Using an Impedance Valve and early Versus Delayed (ROC PRIMED) study, 5% of 13,155 included OHCAs received IO access [14]. On multivariable regression, IO access was associated with decreased probability of ROSC (OR 0.60; 95% CI 0.49 to 0.74), survival (OR 0.44; 95% CI 0.35 to 0.76), and favourable neurological outcome (OR 0.24; 95% CI 0.13 to 0.46); however, this study did not include data on the time of vascular access or the time of first adrenaline use.

In a secondary analysis of the Continuous Chest Compression (CCC) study, which did include time to vascular access and drug administration, IO access was initially attempted in 15.5% of 19,731 OHCA patients [15]. A propensity analysis was undertaken on 2279 patients with initially attempted IO access matched with 2279 patients with initially attempted IV access. In the propensity score matched cohort, the rates of sustained ROSC were significantly lower in the attempted IO group compared with the attempted IV group (18.2% versus 22.5%, p<0.001; adjusted OR 0.72 95% CI 0.61 to 0.85); there was no difference in rates of survival to hospital discharge or survival with favourable neurological outcome. In contrast to several other observational studies, this secondary analysis of the CCC study documented slightly faster time to access and drug administration among those in whom IO was initially attempted. However, among the initial IV attempts, 1178 (7.1%) failed and these patients successfully received IO access. A sensitivity analysis based on eventual successful access showed that patients receiving successful IO access had significantly lower rates of sustained ROSC (adjusted OR 0.73, 95% CI 0.66 to 0.81, p < 0.001), survival to hospital discharge (adjusted OR 0.77, 95% CI 0.63 to 0.93, p = 0.005) and survival with favorable neurological function discharge (adjusted OR 0.73, 95% CI 0.58 to 0.93, p < 0.01) compared with eventual successful IV access. We also assigned the IO and IV groups based on the route that paramedics delivered the study drug, but the methodology of our study is different: we looked for evidence of an interaction in the treatment effect according to whether adrenaline or placebo were administered via the IV or IO routes. The result (interaction p >0.05) in our study did not find evidence of a difference between IV and IO. Thus, the apparent conflict between the results of our study and that of the secondary analysis of the CCC study probably reflects the different methodologies. The inclusion of patients receiving placebo via IO and IV routes may have enabled us to achieve more complete statistical elimination confounding.

A retrospective chart review of three EMS agencies documented that among 1310 OHCA patients receiving adrenaline first via the IO route (48.6%), this route was non-inferior to IV first for the end point of ROSC on emergency department arrival (18.6% versus 20.9%; OR 0.86, 95% CI 0.66 to 1.13) [16]. In this study, the first attempt success rate for IO access was higher than for IV access (94.8% versus 81.6%, p<0.01). Although the site of IO needle placement was not documented, only one of the three EMS agencies allowed humeral head

IO placement; thus, the majority of IO needles were placed in the tibia. In a RCT enrolling 182 OHCA patients, tibial IO access had a higher first-attempt success than either humeral IO or peripheral IV access [12]. We did not document the IO site used in the PARAMEDIC2 study, but it is possible that differences in the IO site used could account partly for some of the variation in results documented in all these observational studies. Among observational studies, we have documented the largest proportion of patients receiving drugs via the IO route, which is probably a reflection of the contemporary cohort of patients in our study against a background of increasing use of the IO route.

Limitations

Our study has several limitations. First, it is a secondary analysis of an RCT, and the route of drug administration was not randomised; thus, we can show only an association between route of drug delivery and the treatment effect. However, we believe that inclusion of placebo groups allowed us to reduce the influence of confounding variables including resuscitation time bias. Second, we have no data on previous attempts at IV access but, given that paramedics were instructed to use the IO route only if the IV route was not possible, it is likely that most of the patients in the IO group had had previous failed attempts at IV access. Third, we were unable to adjust for the unobserved data related to this delay, such as difficulty of access linked to co-morbidities, obesity, vasculopathy, and cause e.g. hypovolaemia. Fourth, for this reason, our study also does not address the question of which access route should be attempted first. Fifth, we did not have information about the IO access site, and this may influence the rate and reliability of delivery of adrenaline. Additionally, the number of survivors at hospital discharge and number with a favourable neurological outcome who received drug via the IO route were small, which limits the precision of our findings. Finally, our study included only adults and therefore there is limited generalisability of findings to children.

Conclusions

In this secondary analysis of the PARAMEDIC-2 trial the treatment effect of adrenaline (versus placebo) on ROSC at hospital handover was the same when given by the IV and IO routes. We could not detect any difference in the treatment effect between the IV and IO routes on the longer-term outcomes of survival to discharge/30 days and favourable neurological outcome at discharge. The results for 30-day survival and survival with a favourable neurological outcome were limited by few events and are therefore inconclusive; an adequately powered study is needed to confirm these findings.

Author contributions

Author Contributions: Perkins, Ji, Lall, Gates and Rogers had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Nolan, Perkins, Deakin, Ji, Lall, Gates

Acquisition, analysis, or interpretation of data: Perkins, Nolan, Deakin, Ji, Lall, Gates, Rosser

Drafting of the manuscript: Nolan, Perkins, Deakin, Ji, Lall.

Critical revision of the manuscript for important intellectual content: Nolan, Perkins, Deakin, Ji, Lall, Gates, Rosser.

Statistical analysis: Ji, Lall, Gates.

Obtained funding: Perkins, Nolan, Deakin, Lall, Gates.

Supervision: Perkins.

Conflict of Interest Disclosures

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the NIHR for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; GDP, CD, JN, have volunteer roles with the

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Role of the Funder/Sponsor

The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer

The views and opinions expressed in this report are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, the NIHR, National Health Service, or the Department of Health and Social Care.

Legends

Figure 1. CONSORT diagram of the analysis by Intravenous and Intraosseous routes.

Figure 2. Adjusted treatment effect and interaction with Intravenous and Intraosseous routes on trial outcomes. Note: *, p-value for treatment and route interaction. Adjustment was made for age, gender, whether a bystander commenced CPR, witness to the arrest, aetiology, initial rhythm, interval between emergency call and ambulance arrival at scene, and interval between ambulance arrival and drug administration.

Figure 3. Cumulative survival to 30 days by treatment and trial drug administration route (upper panel: intravenous route; lower panel: intraosseous route).

Take-home message

In this study there was no significant difference in treatment effect (adrenaline versus placebo) on ROSC at hospital handover whether drugs were administered by the intraosseous or intravenous route. The results for 30-day survival and survival with a favourable neurological outcome were limited by few events and are therefore inconclusive.

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Table 1: Patient characteristics by trial drug administration route type (n=7,317)

	Intravenous (IV) (n=5,080)	**Intraosseous (IO) (n=2,237)**	**Difference (95% CI)**	**P value**
Age				
Mean (SD)	70.9 (15.9)	67.5 (17.5)	3.4 (2.5, 4.2)	<0.001
Median (IQR)	74 (21.5)	70 (26.1)		
Missing	7	2		
Gender				<0.001
Female	1716 (33.8%)	882 (39.4%)		
Male	3364 (66.2%)	1355 (60.6%)		
Missing	0 (0.0%)	0 (0.0%)		
Initial rhythm				<0.001
Shockable rhythm	1031 (20.3%)	318 (14.2%)		
VF	953 (18.8%)	298 (13.3%)		
Pulseless VT	29 (0.6%)	11 (0.5%)		
AED shockable	49 (1.0%)	9 (0.4%)		
Non-shockable rhythm	3970 (78.1%)	1880 (84.0%)		
Asystole	2695 (53.1%)	1319 (59.0%)		
PEA	1205 (23.7%)	530 (23.7%)		

Bradycardia	24 (0.5%)	10 (0.4%)		
AED nonshockable	46 (0.9%)	21 (0.9%)		
Missing	79 (1.5%)	39 (1.7%)		
Aetiology				<0.001
Medical	4713 (92.8%)	2038 (91.1%)		
Traumatic cause	59 (1.2%)	41 (1.8%)		
Drowning	12 (0.2%)	7 (0.3%)		
Drug overdose	72 (1.4%)	65 (2.9%)		
Electrocution	0 (0.0%)	1 (0.0%)		
Asphyxial	126 (2.5%)	56 (2.5%)		
Missing	98 (1.9%)	29 (1.3%)		
Occurrence witnessed				0.004
Unwitnessed	1862 (36.7%)	897 (40.1%)		
EMS witnessed	572 (11.3%)	278 (12.4%)		
Bystander witnessed	2599 (51.2%)	1043 (46.6%)		
Missing	47 (0.9%)	19 (0.8%)		
Bystander commenced CPR				<0.001
Bystander CPR	3100 (61.0%)	1226 (54.8%)		
No bystander CPR	1320 (26.0%)	709 (31.7%)		

Not applicable (for EMS witnessed)	572 (11.3%)	278 (12.4%)		
Missing	88 (1.7%)	24 (1.1%)		
Time from 999 call to treatment				<0.001
<10 min	367 (7.2%)	88 (3.9%)		
10-20 min	2026 (39.9%)	677 (30.3%)		
>20 min	2644 (52.0%)	1460 (65.3%)		
Missing	43 (0.8%)	12 (0.5%)		
Mean (SD)	21.6 (10.5)	25.4 (12.4)	-3.9 (-4.5, -3.3)	<0.001
Median (IQR)	20.4 (10.4)	23.9 (12.6)		
Missing	43	12		
Time from 999 call to At scene (minute)				
Mean (SD)	7.6 (5.8)	7.0 (6.1)	0.6 (0.3, 0.9)	<0.001
Median (IQR)	6.8 (5.7)	6.3 (5.0)		
Missing	0	0		
Time from At scene to Administration of drug (minute)				
Mean (SD)	14.0 (8.6)	18.4 (10.0)	-4.5 (-4.9, -4.0)	<0.001

Median (IQR)	12.7 (8.6)	17.0 (10.5)		
Missing	43	12		
Time on scene				
Mean (SD)	47.4 (21.2)	49.5 (19.5)	-2.1 (-3.7, -0.5)	0.01
Median (IQR)	43.9 (23.2)	46.6 (24.0)		
Not applicable because not transported	2958	1405		
Missing	3	0		
Time transported to hospital				
Mean (SD)	12.9 (9.7)	12.1 (8.7)	0.8 (0, 1.5)	0.04
Median (IQR)	10.7 (8.7)	10.0 (7.9)		
Not applicable because not transported	2958	1405		
Missing	5	0		

Appendix Table 1: Unadjusted summary of outcomes by drug delivery route in (a) Adrenaline arm (b) Placebo arm.

(a)

	Intravenous (IV)	Intraosseous (IO)	p value
Survival at 30 days			
Alive	104/2513 (4.1%)	13/1116 (1.2%)	<0.001
ROSC at hospital handover			
ROSC	668/2488 (26.8%)	189/1111 (17.0%)	<0.001
Survival at hospital discharge			
Alive	102/2510 (4.1%)	12/1115 (1.1%)	<0.001
Favourable neurological outcome at hospital discharge			
Good (0-3)	71/2509 (2.8%)	7/1115 (0.6%)	<0.001

(b)

	Intravenous (IV)	Intraosseous (IO)	p value
Survival at 30 days			
Alive	67/2561 (2.6%)	13/1121 (1.2%)	0.005
ROSC at hospital handover			
ROSC	223/2557 (8.7%)	57/1115 (5.1%)	0.008
Survival at hospital discharge			
Alive	65/2562 (2.5%)	13/1120 (1.2%)	<0.001
Favourable neurological outcome at hospital discharge			
Good (0-3)	53/2561 (2.1%)	11/1120 (1%)	0.02